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ENDGAMES

CASE REPORT

# Plastered in pustules

James Powell *specialist registrar, dermatology*, Jaideep Bhat *consultant dermatologist*, Stephen Orpin *consultant dermatologist*

Dermatology Department, Solihull Hospital, Solihull B91 2JL, UK

An 87 year old woman presented with a non-itchy rash that began three weeks ago on the abdomen. Since then it had spread to most of her trunk, face, and lower limbs. She was not systemically unwell.

Her medical history included atrial fibrillation, cerebrovascular disease, hypertension, and an intertriginous reaction for which oral terbinafine 250 mg daily had been started three days before the rash began. Current long term drugs included aspirin, warfarin, alendronic acid, bisoprolol, calcium supplements, candesartan, furosemide, loperamide, and omeprazole. She had no known drug allergies.

On examination, large confluent patches and plaques of oedematous erythema were present especially on the trunk, face, and lower limbs. The palms and soles were spared. Hundreds of small non-follicular based pustules were seen within these areas. No ulceration or blistering was seen.

Blood tests showed normal renal and liver function, C reactive protein (31 mmol/L; normal 0-1.7), total white cell count (15.7 $\times 10^9$/L; 4.0-11.0), neutrophil count (13.6$\times 10^9$/L; 2.5-7.5), lymphocyte count (1.36$\times 10^9$/L), eosinophil count (0.32$\times 10^9$/L; 0.04-0.44). Haemoglobin and platelet counts were within the normal range.

A swab from a pustule showed no bacterial growth. Histological analysis showed subcorneal pustules.

Terbinafine was stopped immediately and the patient was treated with topical steroids and emollients. The rash began to resolve within a week.

## Questions

1 What is the diagnosis in this case of generalised pustulosis?

2 What is the main differential diagnosis?

3 Can you name three other severe cutaneous drug reactions?

4 How would you manage this patient's rash?

## Answers

### 1 What is the diagnosis in this case of generalised pustulosis?

#### *Short answer*

On the basis of the history and clinical and histopathological findings the diagnosis is acute generalised exanthematous pustulosis.

#### *Long answer*

Acute generalised exanthematous pustulosis is an adverse cutaneous drug eruption in which many small sterile pustules develop within large areas of erythema (figure), often within a few days of starting to take a new drug.

**Fig 1** Small sterile pustules within patches of erythema

More than 90% of cases are caused by a drug and the condition is slightly more common in women than in men.[1 2] The skin reaction often arises rapidly (within hours) on the face, axillae, or groin and then spreads to the rest of the body.[1] The pustules are small "pin head sized" (less than 5 mm), sterile, numerous, and non-follicular; they arise on an oedematous erythema. The eruption may be accentuated in the flexural areas. The mucous

Correspondence to: J Powell jbpowell@doctors.org.uk

membranes are affected only rarely and usually only one site is affected. Fever greater than 38°C often occurs around the onset of the rash.[3] The skin may itch or burn (or both). A peripheral neutrophilia may be present. Just as the skin reaction begins abruptly, resolution typically occurs rapidly after stopping the responsible drug, with no other treatment needed.[1] Complications are rare and tend to occur in people with other comorbidities.[1] An acute generalised exanthematous pustulosis validation scoring system exists.[4]

Although regarded as an uncommon cutaneous drug eruption its incidence may have been under-reported. Acute generalised exanthematous pustulosis—a term first used in 1980—has been known by various terms such as toxic pustuloderma, pustular drug rash, and pustular psoriasiform eruption with leucocytosis, and sometimes it may have been misclassified as generalised pustular psoriasis.[1]

Drugs that are thought to be "highly associated" with the development of this eruption are quinolones, aminopenicillins (amoxicillin and ampicillin), terbinafine, sulphonamides, chloroquine, hydroxychloroquine, diltiazem, and pristinamycin.[1] Less strong associations have been documented with antiepileptics, macrolides, non-steroidal anti-inflammatory drugs, and corticosteroids.[1] Very rarely acute generalised exanthematous pustulosis may be induced by viral infections.[1 2] Hypersensitivity to mercury has also been noted as a precipitating cause.[5]

The timing of onset of the skin reaction in relation to first taking the drug responsible varies. The median onset after taking an antibiotic from the highly associated drug list is one day, whereas for the other drugs in that list it is 11 days.[1]

Histological analysis of pustular lesions in acute generalised exanthematous pustulosis typically shows subcorneal and or intraepidermal pustules, a marked oedema of the papillary dermis, a perivascular infiltrate rich in eosinophils, and single cell necrosis of keratinocytes.[2 4]

The pathogenesis of this reaction is thought to involve drug specific T cells that produce large amounts of interleukin 8, which attract neutrophils.

## 2 What is the main differential diagnosis?

### *Short answer*

Generalised pustular psoriasis.

### *Long answer*

Generalised sterile pustulosis of the skin can also occur in generalised pustular psoriasis. This condition is a severe form of psoriasis and can be triggered by tapering of systemic corticosteroids, pregnancy, infections, and hypocalcaemia. The patient may have a history of (worsening) psoriasis or it may arise de novo.

It is difficult to differentiate between the two conditions clinically. The pustules seen in acute generalised exanthematous pustulosis are clinically indistinguishable from those seen in generalised pustular psoriasis. Crucially, in acute generalised exanthematous pustulosis, patients have usually started taking a new drug. In addition, the pustules are more often seen in the skin folds in acute generalised exanthematous pustulosis than in generalised pustular psoriasis, which causes a more generalised eruption that is more likely to affect the palms and soles and is associated with arthritis in around 30% of cases.[4] Furthermore, in acute generalised exanthematous, the onset and resolution of the eruption and fever are more acute than in generalised pustular psoriasis. Patients with generalised pustular psoriasis are more likely to have a history of psoriasis and have a risk factor for the development of this condition. Generalised pustular psoriasis should be suspected in patients taking a β blocker or angiotensin converting enzyme inhibitor because these drugs are known to induce psoriasis, but are not thought to be major players in the induction of acute generalised exanthematous pustulosis.[4]

Another condition that should be considered if a patient presents with subcorneal pustules on histological analysis is subcorneal pustular dermatosis. In this condition, patients present with flaccid, oval, pea sized pustules in the flexural areas and flexor aspects of the limbs.[5] The face is usually spared. A characteristic finding is that only the lower half of the pustule contains pus, with the upper part containing clear fluid. The condition is benign but chronic, and dapsone is the treatment of choice.

## 3 Can you name three other severe cutaneous drug reactions?

### *Short answer*

Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS).

### *Long answer*

Stevens-Johnson syndrome and toxic epidermal necrolysis are part of a spectrum of conditions characterised by skin tenderness and erythema that evolve into large areas of skin necrosis that cause the epidermis to be sloughed off in sheets. Severe mucosal erosions of the lips, mouth, nose, conjunctiva, and genitals occur alongside the skin blistering. Patients are systemically unwell often with fever, malaise, arthralgia, and myalgia. If skin detachment involves less than 10% of the total body surface area then the diagnosis is Stevens-Johnson syndrome.[6] If 10-30% skin detachment occurs then an overlap between Stevens-Johnson syndrome and toxic epidermal necrolysis can be diagnosed.[6] If more than 30% skin detachment occurs then the diagnosis is toxic epidermal necrolysis.[6] Drugs commonly associated with the development of these conditions include sulphonamides, antimalarials, anticonvulsants, aminopenicillins, non-steroidal anti-inflammatory drugs, and allopurinol. Patients with human immunodeficiency virus infection and certain autoimmune conditions seem to be at greater risk of developing these conditions.

Symptoms of DRESS (drug reaction with eosinophilia and systemic symptoms) typically develop two to six weeks after the responsible drug is taken. A high fever develops, and the initial skin reaction may be maculopapular but can progress to erythroderma.[5] Papules and pustules can develop. Initially, the face, upper trunk, and extremities are usually affected. Facial oedema is often present, and peripheral blood eosinophilia is seen in 90% of cases.[5] Adenopathy, arthritis, arthralgia, and involvement of internal organs can occur. The liver is most commonly affected, and a fatal fulminant hepatitis can develop. Myocarditis, pneumonitis, nephritis, and thyroiditis can also form part of the clinical picture. Treatment is usually with systemic corticosteroids.[5] A scoring system is available to help the clinician decide if this syndrome is "definitely, probably, possibly, or not present." The system is based on features such as fever, adenopathy, organ involvement, eosinophilia, and resolution within 15 days.[7]

## 4 How would you initially manage this patient's rash?

### *Short answer*

Apply greasy emollients to the skin regularly and treat any coexisting infections. Pay meticulous attention to fluid and electrolyte balance, haemodynamic stability, and body temperature. Stop any possible causative drugs immediately.

### *Long answer*

The above measures will help stop progression of the skin reaction, help prevent complications, and provide symptomatic relief. Meticulous attention must be paid to fluid balance, haemodynamic stability, electrolyte imbalances, and body temperature. In all cases of widespread cutaneous eruptions well informed, high quality, constant nursing care is extremely important.

Systemic steroids are not usually needed to treat acute generalised exanthematous pustulosis because the eruption settles once the responsible drug is identified and stopped. Topical care in patients with acute generalised exanthematous pustulosis is very important. The regular application of a greasy emollient such as white soft paraffin:liquid paraffin (50:50) is essential to help maintain the skin barrier. Topical steroids may also help resolve the eruption. Always seek an expert dermatological opinion regarding diagnosis and management, which are often not straightforward.

As this case shows, great care should be taken when prescribing systemic drugs for rashes such as intertrigo in elderly patients who have multiple comorbidities and are taking multiple drugs. Topical treatments are usually effective. Terbinafine is not the treatment of choice for candidiasis, which is often the cause of intertrigenous eruptions.

## Patient outcome

The pustular eruption fully resolved after terbinafine was stopped. She has had no recurrences. Unfortunately, her intertrigo continues to be bothersome and she is being followed up to manage this.

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